REMARKS

Specification

The substituted paragraphs on pages 32, 36, 76, 101, and 102 were amended merely to add SEQ ID NOs in compliance with 37 CFR § 1.821 (d). Marked-up versions of each of these paragraphs are submitted in Appendix A.

The substituted paragraph on page 58 was amended merely to delete a typographical error. A marked-up version of the paragraph is submitted in Appendix A.

No new matter has been added by way of these amendments to the specification.

Sequence Listing:

The sequence listing has been amended to include the sequences of SEQ ID NOs: 58-62, which sequences are found in the originally-filed specification at pages 32, 36, 76, 101 and 102, respectively. No new matter has been added by way of the amendment to the sequence listing.

In compliance with 37 C.F.R §§ 1.821-1.825 and § 1.52(e), the applicants herewith submit the Sequence Listing in written form and computer readable form (3.5 inch disk). The written form and computer readable forms of the Sequence Listing are identical. A statement under 37 CFR § 1.821(f) is submitted herewith.

The Sequence Listing has been generated from the specification and does not constitute new subject matter. The Sequence Listing has been prepared with PatentIn Ver.2.0 and checked with Checker Version 3.0 Program. No error has been found.

Figures

Substitute Figures 1-13 are submitted as formal drawings. Figure 13 was amended merely to include the SEQ ID NO of the sequence shown in the figure in compliance with 37 CFR § 1.821(d).

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The substitute Figures 1-13 and a marked-up version of the originally-filed Figure 13 are attached as Appendix B. No new matter has been added by way of this amendment.

Claims

Claims 1, 2, 25-32 and 35-76 have been cancelled without prejudice as drawn to a non-elected invention. Claim 34 has been cancelled in view of the amendment to claim 33. Claim 3 has been amended merely to remove the reference to non-elected claims 1 and 2 and to substitute the proper SEQ ID NO of the polypeptide. Claim 33 has been amended to recite that the transfected expression vector comprises the polynucleotide of claim 3. Support for the amendments are found throughout the specification and in the originally-filed claims. Marked-up versions of originally filed claims 3 and 33 are attached as Appendix C.

OFFICE ACTION

Allowed Claims

Applicants gratefully acknowledge the allowance of claims 5-7, 10, 13, 16, 20, and 23.

Discussion of the Claim Objections

Claim 3 was objected to because it depends from claims 1 and 2, which are non-elected claims. Claim 3 has been amended to remove reference to claims 1 and 2, as required.

Claim 34 was objected to under 37 CFR 1.75(c) as being in improper form due to multiple dependency. Claim 34 has been cancelled, rendering the objection moot.

It is not clear whether claims 3 and dependent claims 4, 8-9, 11-12, 14-15, 17-19, 21-22 are further objected to. In view of the amendment to claim 3, it is believed that claim 3 and the claims dependent thereon are in proper form.

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Discussion of the 35 U.S.C. § 112 Second Paragraph Rejection

Claim 33 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being incomplete for omitting an essential step. Claim 33 has been amended as suggested by the Examiner, thereby rendering the rejection moot. Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejection.

Discussion of the 35 U.S.C. § 112 Rejection

Claim 18 was rejected under 35 USC § 112, first paragraph, as allegedly not enabled. Applicants respectfully traverse the rejection.

Claim 18 is directed to a novel vector comprising full length ABC1 cDNA, which is designated pCEPhABC1. The pCEPhABC1 plasmid is contains a 10.5 kb insert of human ABC1 cDNA in a commercially available expression vector, pCEPh, which is specifically designed for cloning polynucleotide sequences of interest. The Office argues that claim 18 does not satisfy 35 USC § 112, first paragraph, because the specification does not fully disclose the pCEPhABC1 plasmid sequence, nor is it apparent whether all of the sequences required for its construction are available to the public.

However, contrary to the Office's allegation, the specification fully discloses the entire 10,442 bp ABC1 insert sequence as SEQ ID NO: 1 and further provides the structure of the pCEPhABC1 plasmid in Figure 3. Although the specific nucleotide sequence of the pCEPh cloning vector is not shown, Figure 3 shows the critical functional elements of the pCEPhABC1 plasmid, including the ABC1 insertion sites, the cytomegalovirus promoter site, cloning sites, ABC1 start and stop sites, and restriction sites. Moreover, the pCEPh cloning vector is commercially sold (Invitrogen Corp, Carlsbad, CA cat # VO44-50) and thus the specification need not provide the polynucleotide sequence of the pCEPh cloning vector. Given that the entire sequence of the 10,442 bp ABC1 insert sequence is provided and the pCEPh cloning vector into which the ABC1 sequence is inserted is readily available to the public, the specification adequately describes the structure of the pCEPhABC1 plasmid.

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Further, a deposit is not necessary even though specific biological materials are required to practice the invention if the biological materials can be made or isolated without undue experimentation. MPEP § 2404.02. The law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Further, the fact that experimentation may be complex does not necessarily make it undue. *Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104 (Fed. Cir. 1985); *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

As discussed above, the specification provides the entire 10,442 bp ABC1 insert sequence and teaches the sites of insertion into the pCEPh vector (see Example 4, pages 75-76; Figure 3). Based on this disclosure, one skilled in the art could chemically and/or enzymatically synthesize the ABC1 sequence using routine methods and clone it into the commercially available pCEPh vector. Alternatively, one skilled in the art could screen a normal fibroblast library using the vectors, primers, probes, and methods provided in the specification. Although it is unlikely that screening a library would produce the exact ABC1 clone, using the techniques described in the specification and additional standard cloning, sequencing, and DNA synthesis techniques, one skilled in the art would be able to produce the pCEPhABC1 plasmid without undue experimentation.

For the reasons discussed above, claim 18 is fully enabled by the specification. Accordingly, the Applicants respectfully requests withdrawal of the 35 U.S.C. § 112 rejection.

Discussion of the 35 U.S.C. § 103(a) Rejection

The Office rejected claim 33 under 35 U.S.C. § 103(a) as being obvious over Becq et al., J. Biol. Chem., 272: 2695-2699 (1997). The rejection is respectfully traversed.

Claim 33 as amended is directed to a method for producing an ABC1 protein by transfecting a mammalian host cell with a recombinant expression vector comprising a polynucleotide of specified sequence, i.e., a polynucleotide encoding a polypeptide comprising SEQ ID NO: 2, a

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polynucleotide comprising SEQ ID NO: 1, a polynucleotide comprising nucleotides 291-7074 of SEQ ID NO: 1, and a polynucleotide encoding a polypeptide having at least 98% sequence identity with SEQ ID NO: 2.

Thus, to establish a *prima facie* case of obviousness, the Office must show: (1) a teaching or suggestion to produce an ABC1 protein in a mammalian host cell using a recombinant expression vector comprising one of the specified polynucleotides and (2) a reasonable expectation of success of producing the ABC1 protein. The teaching or suggestion to use a recombinant expression vector comprising one of the specified polynucleotides to produce the ABC1 protein and the reasonable expectation of its success must *both* be found in the prior art, and must *not be based on applicant's disclosure. In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2143.

The Office argues that one skilled in the art would have been motivated to make an ABC1 cDNA and subclone it into an expression vector based on the teachings of Becq et al. which teach the *in vitro* production of ABC1 protein using cRNA which is injected into frog oocytes. Further, the Office states that one of ordinary skill in the art would have a reasonable expectation of success since Becq et al. provide the cRNA or the mRNA encoding the protein and it is common knowledge to synthesize the cDNA and express it in a cell.

However, Becq et al. employs a different ABC1 polynucleotide in its frog oocyte system, and further does not teach or suggest the ABC1 polynucleotides used in the presently claimed method. Given that Becq et al. does not teach or suggest a polynucleotide encoding a polypeptide comprising SEQ ID NO: 2, a polynucleotide comprising SEQ ID NO: 1, a polynucleotide comprising nucleotides 291-7074 of SEQ ID NO: 1, or a polynucleotide encoding a polypeptide having at least 98% sequence identity with SEQ ID NO: 2, Becq et al. certainly does not teach or suggest a method of producing an ABC1 protein using a recombinant expression vector comprising any of these specified polynucleotides.

For the reasons provided, Becq et al. does not render obvious the method of claim 33. Accordingly, Applicants respectfully request withdrawal of the 35 USC 103 § rejection.

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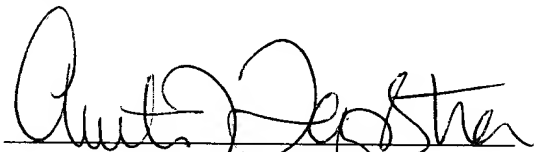
Conclusion

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Date: December 18, 2002

By: 
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Appendix A

Marked-up copy of the specification amendments

Page 32, third paragraph:

In one preferred embodiment, the isolated polynucleotide comprises a nucleotide sequence encoding the polypeptide comprising SEQ ID NO: 2. Importantly, in contrast to the published sequence of Langmann et al. which codes for a protein of 2201 amino acids based on a predicted start methionine found in exon 3 (Langmann et al., *Biochem. Biophys. Res. Comm.*, 257: 29-33 (1999) (GenBank Accession No. AJO12376), the presently claimed nucleotide sequence contains 50 exons and codes for a protein of 2261 amino acids (see Figure 4). The corresponding nucleotide sequence of the present invention contains a coding sequence that includes an additional 180 nucleotides at the 5' end corresponding to the following 60 amino-terminal amino acids: MACWPQLRLLLWKNLTFRRRQTCQLLLEVAWPLFIFLILISVRLSYPPYEQHECH FPNKA **(SEQ ID NO. 58)**. Given that there is an in-frame stop codon 6 to 9 nucleotides upstream from this location, the newly predicted start site is the first methionine codon that could produce a continuous open reading frame. Alignment of this new ABC1 cDNA sequence with related ABC transporter sequences ABCR and ABC-C (also known as ABC3) which also contain open reading frames for

Page 36, third paragraph:

In another embodiment, the isolated polynucleotide comprises the 3' flanking region of ABC1. Several 3' untranslated regions have been identified which may represent alternate sites of polyadenylation of the ABC1 transcript. Preferably, the 3' flanking region contains regulatory sequences. For example, the full length 3' UTR (SEQ ID NO: 6) contains 46 sequences (AA)nCU/UC(AA)n **(SEQ ID NO: 59)** which have

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been shown to be necessary for binding of Vigilin. Vigilin, a ubiquitous protein with 14K homology domains, is the estrogen-inducible vitellogenin mRNA 3'-untranslated region binding protein (*J. Biol. Chem.*, 272: 12249-12252 (1997)). In addition to binding HDL, Vigilin has been shown to bind to the 3' flanking region of mRNAs and to increase the half-life of the mRNA transcript (*Mol. Cell. Biol.*, 18:3991-4003 (1998)). Thus, the 3' flanking region could be altered, for example, to increase the binding of Vigilin, thereby increasing the half-life of the ABC1 mRNA. Preferably, the isolated polynucleotide comprises

Page 58, second paragraph:

The dosage regimen for treating a cardiovascular disease with a composition comprising an ABC1 polynucleotide or ABC1 expression vector is based on a variety of factors, including the type of cardiovascular disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. For example, the amount of ABC1 polynucleotide or ABC1 expression vector to be administered is an amount sufficient to increase cholesterol efflux from the cells of a mammalian subject. Such amount can be determined, for example, by measuring the plasma HDL-cholesterol level of a subject before and after administration of the ABC1 polynucleotide or ABC1 expression vector. A sufficient amount of ABC1 polynucleotide or ABC1 expression vector is an amount that increases the plasma HDL-cholesterol level of a subject. Accordingly, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about [?]0.1 g/kg to about 100 mg/kg or more, depending on the factors mentioned above."

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Page 76, first paragraph:

against a synthetic peptide corresponding to KNQTVVDAVLTSFLQDEKVKES **(SEQ ID NO. 60)** located at the C-terminus, as described in Example 11. The anti-ABC1 antibodies can be detected using several methods known in the art, including, for example, western blotting, immunoprecipitation, and FACS, wherein the detection can be accomplished using radioactive, colorometric, or fluorescent labeling. One preferred method for measuring the amount of ABC1 protein in a cell sample is immunoprecipitation, wherein biotinylated ABC1 proteins are contacted with anti-ABC1 antibody and the bound anti-ABC1 antibody is detected using streptavidin horse radish peroxidase.

Page 101, fourth paragraph:

To determine which portion of the 5' flanking region of ABC1 retains transcriptional activity in response to nuclear ligands, various plasmids containing a different portion of the 5' flanking region and a luciferase reporter gene were transfected into RAW 264.7 cells treated with at least one ligand for the nuclear receptors. Using this system, an sterol response element corresponding to nucleotides 1480-1510 of SEQ ID NO: 3 was identified. The sterol response element contains a direct repeat-4 element TGACCGatagTAACCT **(SEQ ID NO: 61)**. Confirmation of the sterol response element was obtained using site-directed mutagenesis and band-shift assay techniques.

Page 102, third paragraph:

Site-Directed Mutagenesis: The sterol response element corresponding to nucleotides 1480-1510 of SEQ ID NO: 3 was mutated in the 1080-1643 sequence described above using site-directed mutagenesis. Specifically, the response element containing a direct repeat-4 element TGACCGatagTAACCT **(SEQ ID NO: 61)** was

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mutated to **CTGCACatagTAACCT (SEQ ID NO: 62)** using the GeneEditor system (Promega, Madison, WI) according to the manufacturer's protocol.

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Appendix C

Marked-up copy of the claim amendments

Claim 3. (Amended) An isolated polynucleotide selected from the group consisting of a polynucleotide encoding [the] a polypeptide [of claim 1] comprising SEQ ID NO: 2, a polynucleotide comprising SEQ ID NO: 1, a polynucleotide comprising nucleotides 291-7074 of SEQ ID NO: 1, and a polynucleotide encoding [the] a polypeptide [of claim 2] having at least 98% sequence identity with SEQ ID NO: 2.

Claim 33. (Amended) A method for producing an ABC1 protein in a mammalian host cell comprising the steps of:

(a) transfecting the mammalian host cell with a recombinant expression vector comprising [a] the polynucleotide [encoding ABC1] of claim 3 in an amount sufficient to produce a detectable level of ABC1 protein; [and]

(b) culturing the transfected host cell in step (a); and

(c) purifying the produced ABC1 protein.

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